

REC'D 31 OCT 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference RJG/JLB/1797-PCT	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/02788	International filing date (day/month/year) 19/07/2000	Priority date (day/month/year) 21/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant FUJISAWA PHARMACEUTICAL CO LTD et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 7 sheets, including this cover sheet.
  - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  07/02/2001	Date of completion of this report  29.10.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Hornich, E  Telephone No. +49 89 2399 8721  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02788

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-6 as originally filed

**Claims, No.:**

1-6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02788

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 2, 6.

because:

- ☒ the said international application, or the said claims Nos. 2, 6 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims
	No: Claims 1-6
Inventive step (IS)	Yes: Claims
	No: Claims -
Industrial applicability (IA)	Yes: Claims 1, 3-5

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/02788

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No: Claims

2. Citations and explanations  
see separate sheet

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
see separate sheet

### SECTION III

1. Claims 2 and 6 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

### SECTION V

2. Reference is made to the following documents:

**D1:** WO 91 04025 A

**D2:** US-A-5 648 351

**D3:** WO 93 14771 A

**D4:** WO 94 04148 A

**D5:** BEERS, M. H., BERKOW, R.: 'The Merck Manual of Diagnosis and Therapy', 1999, MERCK RESEARCH LABORATORIES, N.J.

The document **D5** was not cited in the international search report.

3. Novelty (Art. 33(2) PCT)

- 3.1 Document **D1** describes the use of the *compound of the present invention* for the treatment of *immunodepression*, included e.g. *senile dementia* and *certain central nervous system disorders* (see: p. 4, l. 9-12; p. 11, l. 11-15; p. 13, l. 14-25; p. 33, ex. 20; p. 37, l. 20-24 (cl. 6)).

As, according to the disclosures within **D1**, the *use* of the compound of the formula I (present application) *in medical treatment* is already *known*, the subject-matter of claims 3-5 of the present invention, formulated as '*first medical use*' - claims, is **not novel**.

**D3** and **D4** also describe the *medical use* of the *compound of the present application* for the treatment of *airway diseases* respectively *AIDS*, therefore also **anticipating**

the subject-matter of claims 3-5 (D3: claim 1, p. 10, l. 22-24; D4: claims 1 and 4).

- 3.2 Dementia, included in the disorders within D1, is *associated with loss / degeneration of neurons* in the brain (see D5, p. 1393-1399, esp. p. 1396, left col., 'pathogenesis' and p. 1398, right col., 'Non-Alzheimer's Dementias'); therefore, the teaching within D1 is also **prejudicial to the novelty of claims 1, 2 and 6**.

Accordingly, claims 1-6 cannot be regarded **novel**.

4. It is furthermore pointed to document D2:

D2 discloses compounds (the *compound of the present application comprised* in the Markush-formula, but *not explicitly mentioned*), for the treatment of *cerebral ischemic diseases*, such as *brain damage* caused by *ischemia* or *cerebral infarction* (see the *abstract*, col. 6, l. 21f. and l. 48-67; col. 7, l. 37f.; col. 8, l. 22-30; claim 1, in context with col. 2, l. 10 and col. 4, l. 11).

The pharmacological *test* appears to be the same as or at least very similar to that in the present application, thus probably being carried out with regard to the same or similar effects (concerning the pharmacological profile) as in the present application.

5. Industrial Applicability (Art. 33(4) PCT)

For the assessment of the present claims 1-6 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

## SECTION VIII

6. Formulations as in claim 1, 'use of ... for manufacturing a *neuroprotective agent*', are considered by this Authority as claims for the first medical use of an active compound, since the *intended use* ('neuroprotective agent') should be disregarded within the examination of a European Patent Application.

However, in interpreting claims for determining novelty and inventive step, the subject-matter of claim 1 is regarded as 'a use of a compound ... for manufacturing an agent *for the prevention or treatment of acute or chronic cerebral neurodegenerative diseases*' (second medical use), corresponding to the probable intention of the Applicant, as '*acute or chronic cerebral neurodegenerative diseases*' are part of the subject-matter of claims 2-6.

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>RJG/1797 PCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 00/ 02788</b>	International filing date (day/month/year) <b>19/07/2000</b>	(Earliest) Priority Date (day/month/year) <b>21/07/1999</b>
Applicant  <b>FUJISAWA PHARMACEUTICAL CO LTD</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**NEW USE OF A MACROLIDE COMPOUND FOR TREATING NEURODEGENERATIVE DISORDERS.**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.



# INTERNATIONAL SEARCH REPORT

Intern: 1st Application No

PCT/GB 00/02788

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/44 A61P25/28 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, SCISEARCH, BIOSIS, MEDLINE, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 648 351 A (KELLY JOHN S ET AL) 15 July 1997 (1997-07-15) column 3, line 65 - column 4, line 20	3-5
X	WO 91 04025 A (FISONS PLC) 4 April 1991 (1991-04-04) page 37, line 20 - line 24 page 13, line 14 - line 25 claims 1,6	3-5
X	WO 93 14771 A (FISONS PLC) 5 August 1993 (1993-08-05) claim 8 page 10, line 22 - line 24	3-5
X	WO 94 04148 A (FISONS PLC) 3 March 1994 (1994-03-03) claims 4,1	3-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

26 January 2001

Date of mailing of the international search report

01/02/2001

Name and mailing address of the ISA

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 NL - 2280 HV Rijswijk  
 Tel (+31-70) 340-2040, Tx. 31 651 epo nl.  
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Authorized officer

Bonzano, C

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/02788

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5648351 A	15-07-1997	AU 687025 B	19-02-1998
		AU 5716094 A	19-07-1994
		CA 2152803 A	07-07-1994
		CN 1103580 A, B	14-06-1995
		EP 0676961 A	18-10-1995
		WO 9414443 A	07-07-1994
		JP 8505136 T	04-06-1996
WO 9104025 A	04-04-1991	CA 2065425 A	15-03-1991
		EP 0491797 A	01-07-1992
		GR 90100688 A, B	20-01-1992
		IE 903334 A	10-04-1991
		JP 5500215 T	21-01-1993
		PT 95305 A	25-06-1991
WO 9314771 A	05-08-1993	AU 3456793 A	01-09-1993
		ZA 9300691 A	06-09-1993
WO 9404148 A	03-03-1994	AU 4967193 A	15-03-1994
		MX 9305152 A	31-05-1994
		ZA 9306137 A	21-02-1994

# PATENT COOPERATION TREATY

PCT

## NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU OF PATENT COOPERATION

To:

GAUNT, Robert, John  
Stevens Hewlett & Perkins  
Halton House  
20/23 Holborn  
London, Greater London EC1N 2JD  
ROYAUME-UNI

STEVENS HEWLETT  
& PERKINS

RECEIVED

- 2 FEB 2001

DIA

FILE

No.

Date of mailing (day/month/year) 25 January 2001 (25.01.01)		
Applicant's or agent's file reference RJG/1797 PCT		IMPORTANT NOTICE
International application No. PCT/GB00/02788	International filing date (day/month/year) 19 July 2000 (19.07.00)	Priority date (day/month/year) 21 July 1999 (21.07.99)
Applicant FUJISAWA PHARMACEUTICAL CO LTD et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES,  
FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,  
MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,  
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 25 January 2001 (25.01.01) under No. WO 01/05385

### REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

### REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

COPIED TO BRISTOL

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Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number  
**WO 01/05385 A3**

- (51) International Patent Classification<sup>7</sup>: **A61K 31/44**,  
A61P 25/28, 25/00
- (74) Agents: GAUNT, Robert, John et al.; Stevens Hewlett  
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London EC1N 2JD (GB).
- (21) International Application Number: PCT/GB00/02788
- (22) International Filing Date: 19 July 2000 (19.07.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
9917158.9 21 July 1999 (21.07.1999) GB
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,  
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (71) Applicant (*for all designated States except US*): FU-  
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541-8514 (JP).
- (84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): JONES, Paul,  
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- Published:  
— with international search report
- (88) Date of publication of the international search report:  
2 August 2001
- For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: NEW USE OF A MACROLIDE COMPOUND FOR TREATING NEURODEGENERATIVE DISORDERS

(57) Abstract: Macrolide compound, such as a tacrolimus analogue is provided for use as a neuroprotective agent, particularly, for preventing or treating acute or chronic cerebral neurodegenerative diseases.

WO 01/05385 A3

NEW USE OF A MACROLIDE COMPOUND

## TECHNICAL FIELD

This invention relates to a new use of a macrolide compound.

## BACKGROUND ART

A certain macrolide compound, i.e., tacrolimus, and its related compounds are known to have preventing or treating activity of cerebral infarction (USP 5,648,351). However, it is desirable to provide more effective and/or safer drug with a superior pharmaceutical profile against cerebral ischemic disease.

## DISCLOSURE OF INVENTION

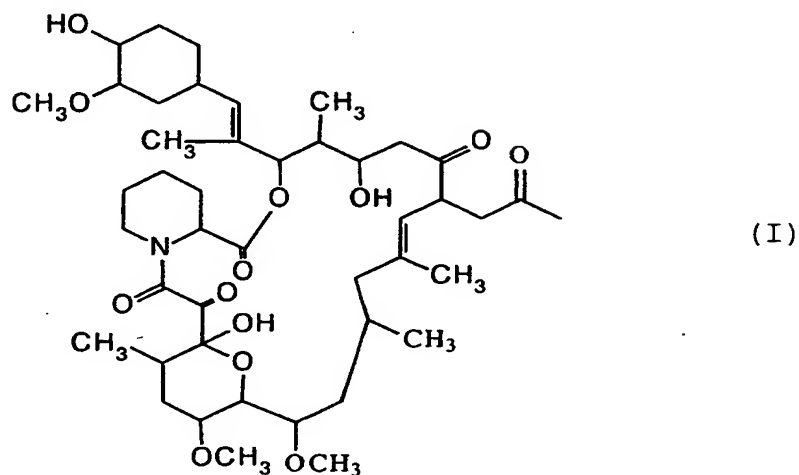
The inventors of this invention have found that one of the tacrolimus analogues, i.e., a compound (I), mentioned below, has an excellent neuroprotective efficacy.

Accordingly, this invention provides a new use of the compound (I) as a neuroprotective agent.

Further, this invention provides a neuroprotective agent, which comprises the compound (I).

Still further, this invention provides a method for preventing or treating acute or chronic cerebral neurodegenerative diseases, which comprises administering said compound (I) to mammals.

The tacrolimus analogue used in the present invention has the following chemical formula.



It has already been produced in USP 5,376,663, example 29.

With respect to the compound (I) used in the present invention, it is to be understood that there may be conformers and one or more stereoisomers such as optical and geometrical isomers due to asymmetric carbon atom(s) or double bond(s), and such conformers and isomers are also included within the scope of the compound in the present invention. And further, the compound can be in the form of a solvate or pro-drug, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

The compound (I) usable in the present invention may be administered as pure compound or mixture of compound or

preferably, in a pharmaceutical vehicle or carrier.

The compound (I) in this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the compound(I), as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external(topical), enteral, intravenous, intramuscular, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable, carriers for tablets, pellets, capsules, eye drops, suppositories, solutions (saline, for example), emulsion, suspensions (olive oil, for example), ointment, aerosol sprays, cream, skin plasters, patches and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the disease.

Mammals which may be treated using the method of the

present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans.

For applying this composition to a human, it is preferable to apply it by injection.

While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.0001-1000 mg, preferably 0.001-500 mg and more preferably 0.01-100 mg. of the active ingredient is generally given for treating diseases, and an average single dose of about 0.001-0.01mg, 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered. Daily doses for chronic administration in humans will be in the range of about 0.1-30 mg/kg/day.

And further, the compound (I) can be applied, simultaneously, separately or sequentially, with other agents having neuroprotective activity, such as thrombolytics (e.g., tPA, urokinase, etc), fibrinolytics, platelet inhibitors and so on.

The following examples illustrate the present invention in further detail. It should be understood that those examples are not intended to limit the scope of the invention.

#### Example 1

Neuroprotective efficacy of the compound (I) in the rat



endothelin-induced MCA occlusion model

(1) METHOD

The compound (I) was dissolved in a polyoxyethylene-hydrogenated castor oil 60/ethanol (400mg/1ml) solution and administered at 1 and 3 mg.kg<sup>-1</sup>. All drugs and relevant control were administered in a volume of 2 ml.kg<sup>-1</sup>. MCA occlusion by the endothelin method was performed on male Sprague Dawley rats (271 - 324g) as described in USP 5,648,351. All drugs were infused through the i.v. catheter at 1 ml min<sup>-1</sup>, five minutes post-lesion. The animals were sacrificed by cardiac infusion under barbiturate anaesthesia. Volume of lesion was calculated from measured areas of damage (as assessed three days post-lesion) using the Trapezoid Rule. Results are presented as volume (mm<sup>3</sup>) ± SEM. Statistical analysis was performed using ANOVA and post hoc Student-Newman-Keuls test, where p < 0.05 was set as an acceptable level for significance.

(2) RESULT

Protection in the ET-1 model of stroke by the compound (I) at 1 mg.kg<sup>-1</sup> (n=14) and 3 mg.kg<sup>-1</sup> (n=9) against vehicle (n=11) was studied. The compound (I) protected the cortex 61% and 42% respectively at both 1 and 3 mg.kg<sup>-1</sup>.

The compound (I) was proved to have a neuroprotective

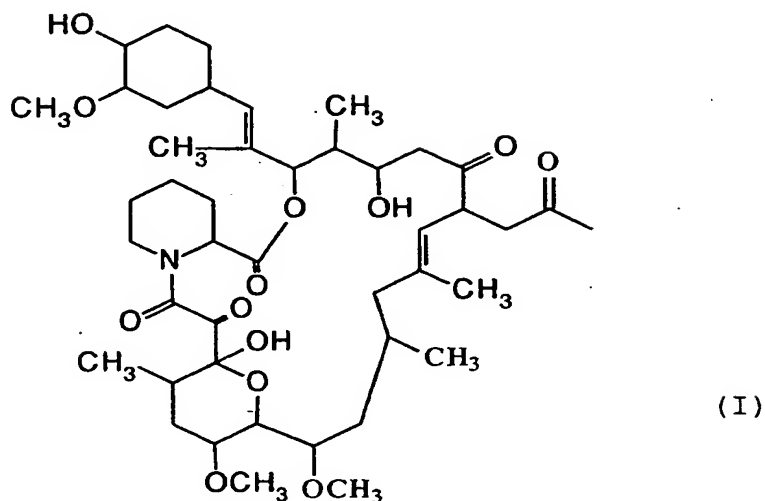
efficacy, though it has no immunosuppressive activity. So, the present invention provides useful neuroprotective agent for preventing or treating acute or chronic cerebral neurodegenerative diseases, such as brain damage caused by ischemia or hemorrhage, etc.

So, it is useful when the following diseases or injury occur; that is, cerebral infarction, hemorrhage infarct, multi-infarct dementia, head injury, hemorrhage in brain such as subarachnoid hemorrhage or intracerebral hemorrhage, cerebral thrombosis, cerebral embolism, cardiac arrest, stroke (such as, acute, subacute, or chronic stroke), transient ischemic attacks (TIA), hypertensive encephalopathy, etc.

The patents, patent applications and publications cited herein are incorporated by reference.

CLAIMS

1. A use of a compound of the following formula:



for manufacturing a neuroprotective agent.

2. A method for preventing or treating acute or chronic cerebral neurodegenerative diseases, which comprises administering the compound (I) identified in Claim 1 to mammals.
3. A pharmaceutical composition for preventing or treating acute or chronic cerebral neurodegenerative diseases, which comprises compound (I) in admixture with a carrier or excipient.
4. The composition in Claim 3, in which the cerebral neurodegenerative diseases is brain damage caused by ischemia or hemorrhage.
5. The composition in Claim 4, in which the cerebral neurodegenerative diseases is cerebral infarction.

6. A use of the compound (I) for preventing or treating acute or chronic cerebral neurodegenerative diseases.

# INTERNATIONAL SEARCH REPORT

Intern: 1al Application No

PCT/GB 00/02788

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/44 A61P25/28 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, SCISEARCH, BIOSIS, MEDLINE, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 648 351 A (KELLY JOHN S ET AL) 15 July 1997 (1997-07-15) column 3, line 65 -column 4, line 20	3-5
X	WO 91 04025 A (FISONS PLC) 4 April 1991 (1991-04-04) page 37, line 20 - line 24 page 13, line 14 - line 25 claims 1,6	3-5
X	WO 93 14771 A (FISONS PLC) 5 August 1993 (1993-08-05) claim 8 page 10, line 22 - line 24	3-5
X	WO 94 04148 A (FISONS PLC) 3 March 1994 (1994-03-03) claims 4,1	3-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

26 January 2001

Date of mailing of the international search report

01/02/2001

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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